REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised to define the invention with additional clarity. The revision of claim 30 finds support at the top of page 12 of the subject specification. Claim 39 has been cancelled. The newly presented claims find support throughout the disclosure and in the same manner as the claims from which they depend.

The Examiner is again urged to reconsider the requirement for restriction for the reasons that follow.

In maintaining the requirement for restriction, the Examiner comments (top of page 3 of the Action) that an examiner "may raise a lack of unity issue during national stage phase on his discretion". It appears that the Examiner has misinterpreted the MPEP section quoted at the bottom of page 2 of the Action, that is, the Examiner appears to overlook the fact that what is required as a threshold matter is that the Examiner find lack of unity under Section 1.475. Respectfully, it is submitted that no lack of unity should have been found for the reasons that follow.

The present invention relates to conjugates comprising a bioreductive moiety linked to a therapeutic agent. As described more fully below, the conjugate is such that on bioreduction (of the bioreductive moiety) the latter is converted into a 'form' that is capable of undergoing a 'through-bond' elimination reaction to release the therapeutic

agent from the conjugate. The bioreduction may, for example, occur at a site of hyp xic or ischaemic tissue so that there is localized delivery of a therapeutic agent to that tissue.

As it is understood, the Examiner has limited consideration to the subject matter of Group I (claims 24-30, 32 and 37-45), the species wherein R_1-R_3 are each hydrogen, R_4 is alkyl and the linker is -NH-. The Examiner's basis for restriction results from the fact that the Examiner is of the view that that no generic claim is allowable. Applicants respectfully disagree. The cited art is not relevant to claim 24, much less claim 29 (from which claim 30 depends).

Claim 24 covers a bioreductive conjugate comprising at least one therapeutic agent linked to a bioreductive moiety, the latter incorporating an aromatic ring substituted with a nitro group. It is a requirement of claim 24 that, on bioreduction, the nitro group (of the bioreductive moiety) causes release of the therapeutic agent **by a through bond elimination** and the residue of the bioreductive moiety undergoes an intramolecular cyclization reaction in which the nitrogen of the original nitro group provides an atom of the thus formed ring.

The principle of through bond elimination is illustrated in Schemes 1 and 2 as shown on pages 6 and 7 of the subject specification. It will be seen from these Schemes that bioreduction of the nitro group leads to a group of the formula -NHZ (where Z is H or OH). The lone-pair of electrons on the nitrogen atoms of -NHZ initiates release of th therapeutic agent by displacement of electrons along a chemical bond system connecting the –NHZ group and the therapeutic agent. With release of the therapeutic agent there is

then an intramolecular cyclization of the residue of the bioreductive moiety in which the nitrogen atom of these –NHZ group forms part of the ring that is generated.

Noteworthy is the 'similarity' between the first structure shown in Scheme 1 on page 6 and the formulae included in at least claims 29 and 30 of the subject application.

In summary, therefore, bioreduction of the conjugate causes the therapeutic agent to be released by virtue of a **through bond elimination**.

The cited art neither teaches nor suggests Applicants invention. Given the single inventive concept that underlies the invention, no lack of unity should have been found. Accordingly, reconsideration and withdrawal of the requirement for restriction (at least to the extent that consideration is given to the conjugate of claim 29) is requested.

Claims 30, 37 and 39-45 stand rejected under 35 USC 112, second paragraph. Withdrawal of the rejection is submitted to be in order in view of the above claim revisions. Reconsideration is requested.

Claims 24-28 and 37-45 stand rejected under 35 USC 102 as allegedly being anticipated by Rauth; claims 24-28, 37 and 38 stand rejected under 35 USC 102 over Hay et al; and claims 24-28 and 37-45 stand rejected under 35 USC 102 over Adams et al. The rejections are traversed for the reasons that follow (it is noted that neither claim 29 nor claim 30 is included in these rejections).

Applicants submit that Rauth et al does not disclose the compounds of claim 24. The Examiner has referred to two compounds in Figure 8, namely Nitracrine and Nitraquine (these being the left and center compounds in the row f three compounds in

Fig. 8). However, thes compounds do not include a bioreductive moiety and a therapeutic agent linked thereto nor are the molecules such that a through bond elimination reaction could be effected. The Examiner has also referred to Figs. 5 and 6 of Rauth. However, there does not seem to be any form of through bond elimination in Fig. 5 and it is in fact difficult to determine what the elimination might be in that Figure. With regard to Fig. 6, there is an elimination reaction, e.g., in going from compound (1) to compound (3) or from compound (2) to compounds (4) but this appears to be a 'through space' elimination. It is also noteworthy that the two reactions mentioned are in fact 'unwanted' reactions. The desired reaction in Fig. 6 is that at the left hand side of the figure showing conversion of the compound SN23682 to compound (6). This does not involve elimination and, more specifically, does not relate to a bioreductive conjugate in which a bioreductive carrier is linked to a 'releasable' therapeutic agent.

Hay et al postulates bioreductive conjugates incorporating at least one therapeutic agent having linked thereto a bioreductive moiety incorporating an aromatic ring substituted with a nitro group. Furthermore, it is postulated in Hay et al that reduction of the bioreductive moiety results in release of the therapeutic agent with the residue of the bioreductive moiety undergoing an intramolecular cyclisation reaction. To that extent the disclosure of Hay et al is similar to the present invention but there the similarity ends. In Hay et al, release of the therapeutic agent occurred via a **through space** "attack" of the reduced form of the nitrogen group on a carbonyl group to form a lactam with release of the therapeutic agent. This mechanism is clearly shown for the compound designated (II)

(i.e. the reduced form of the bi reductive conjugate (I)) with ultimate formation of the lactam (IV). Therefore, Hay et a only discloses bioreductive conjugates in which release of the therapeutic agent occurs by a **through space** cyclization and not a **through bond** elimination as required by present claim 24.

Adams et al is also not seen to be relevant to claim 24. Adam et al discloses treatment of solid tumors with two compounds, namely (i) a bioreductive drug of the formula defined at the foot of column 1, and (ii) a nitric oxide (NO) synthase inhibitor. The compounds may be administered separately or as an admixture. The Examiner's argument is that the NO synthase inhibitors themselves fall within the definition of claim 24 of the present application. That said, the bioreductive drugs (i) are *prima facie* more similar to the compounds of claim 24 of the present application than are the NO synthase inhibitors on which the Examiner relies. The compounds (i) are defined in the paragraph bridging columns 1 and 2 of Adam et al but these compounds would not be capable of undergoing a through bond elimination reaction on reduction of the nitro group of the imidazole/triazole ring to which it is bonded. The detailed description of the NO synthase inhibitors begins at the foot of column 12 of Adam et al (the Examiner's reference to 'Col 10, 2nd Col' is not understood). Specific NO synthase inhibitors are described in column 14 but are not conjugates as defined in claim 24 of the present application. More particularly, they do not incorporate a 'releasable' drug and none of the NO synthase inhibitors described have (in the definitions of the 'variable' components (e.g. the R groups) an aromatic ring substituted with a nitro group. There is

a reference at column 15 lines 21-26 to 7-nitro indazole and derivatives thereof as NO synthase inhibitors. However these compounds do not include a therapeutic agent nor are they capable of undergoing a through bond elimination reaction on reduction of the nitro group. The description at column 16, lines 33-60 to which the Examiner has referred merely talks about type of formulations to be administered for effecting the treatment of Adam et al. There is nothing more relevant in the Examples to which the Examiner has referred. Respectfully, basis for the Examiner's reliance on Adam et al is unclear, still less clear is why the Examiner believes that the NO synthase inhibitors discloses therein meet the limitations of claim 24.

In view of the above, reconsideration is requested.

Claims 24-30, 32 and 37-45 stand rejected under 35 USC 103 a allegedly being obvious over Rauth et al. The rejection is traversed.

Respectfully, it is not clear to which of Rauth's compounds the Examiner is referring. In fact, Applicants cannot see in Rauth a compound that would 'match' the Examiner's objection to claim 29 which is that Rauth's reductive entity is 'shorter by one carbon **chain**' (emphasis added).

Claim 29 defines a structure in which there is an aromatic system with a substituent incorporating at least one olefinic double bond conjugated to the aromatic system (since n is 1-3). This double bond is important in the compound as defined in claim 29 because it provides for the through bond elimination reaction (see the reaction scheme on page 6 of the present specification). None of the compounds disclosed by

Rauth incorporates an aromatic system substituted with a nitro group and a side chain incorporating an olefinic double bond, as defined in claim 29. As indicated, this double bond is important in effecting the through bond elimination of the drug. There is thus no suggestion of this structure in the disclosure of Rauth. The only one of Rauth's compounds with an olefinic double bond conjugated to an aromatic system appears to be that in Fig. 10 but there is no nitro group bonded to the aromatic ring.

If the Examiner's contention is that it would be obvious to add to any of Rauth's compounds which do incorporate an aromatic nitro group a side chain with an olefinic double bond conjugated to the aromatic ring (as defined in claim 29), then it is submitted that there is no basis for such an assertion. If the Examiner's argument is that the side chain (with its conjugated double bond) of claim 29 is 'immaterial' to the compounds and could simply be omitted to arrive at something approximating to a compound shown in Rauth, then this is a fundamental misunderstanding on the part of the Examiner since, as indicated, the side chain is required for the through bond elimination. In either case, the rejection is not well founded and should be withdrawn.

Reconsideration is requested.

Submitted herewith is a PTO-1449 Form listing documents cited in the International Search Report. The Examiner is requested to initial and return same (the Notification of Acceptance indicates copies of the references have been received).

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

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Respectfully submitted,

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